(e) *Exemptions.* This section does not apply to estrogen-progestogen oral contraceptives. Labeling requirements for these products are set forth in § 310.501.

(f) *Requirement to supplement approved application.* Holders of approved applications for estrogen drug products that are subject to the requirements of this section must submit supplements under § 314.70(c) of this chapter to provide for the labeling required by paragraph (a) of this section. Such labeling may be put into use without advance approval by the Food and Drug Administration.

[55 FR 18723, May 4, 1990]

§ 310.516 Progestational drug products; labeling directed to the patient.

(a) The Commissioner of Food and Drugs concludes that the safe and effective use of any progestational drug product requires that patients be informed that there is an increased risk of birth defects in children whose mothers have taken this drug during the first 4 months of pregnancy. Accordingly, except as provided by paragraph (d) of this section, any progestational drug product that is the subject of a new drug application approved either before or after October 9, 1962 and all identical, related, or similar drug products as defined in § 310.6, whether or not the subject of an approved new drug application, shall be dispensed to patients with labeling in lay language containing such a warning. The patient labeling shall be provided as a separate printed leaflet independent of any additional materials.

(b) The patient labeling shall specifically include the following:

(1) Name of the drug.

(2) Name and place of business of the manufacturer, packer, or distributor.

(3) A warning that there is an increased risk of birth defects in children whose mothers take this drug during the first 4 months of pregnancy.

(4) A brief discussion of the nature of the risks of birth defects resulting from the use of these drugs during the first 4 months of pregnancy.

(5) A brief statement that these drugs are no longer considered safe as a test for pregnancy.

(6) A statement that the patient should inform her physician as soon as possible if she discovers that she was pregnant when she took the drug.

(c) The patient labeling shall be printed in accordance with the following specifications:

(1) The minimum letter size shall be one-sixteenth of an inch in height.

(2) Letter heights pertain to the lower-case letter ''o'' or its equivalent that shall meet the minumim height standard.

(3) Type used shall conform to the minimum letter height. The body copy shall contain 1-point leading, noncondensed type, and shall not contain any light-face type or small capital letters.

(d) This section does not apply to a progestogen-containing product intended for contraception, which shall be labeled according to the requirements of § 310.501.

(e)(1) Patient labeling for each progestational drug product shall be provided in or with each package intended to be dispensed to the patient. Patient labeling for drug products dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before first administration of the drug and every 30 days thereafter, as long as the therapy continues.

(2) In the case of progestational drug products in bulk packages intended for multiple dispensing, a sufficient number of patient-labeling pieces shall be included in or shall accompany each bulk package to assure that one can be included with each package dispensed to every patient. Each bulk package shall be labeled with instructions to the dispenser to include one patient-labeling piece with each package dispensed to the patient. This section does not preclude the manufacturer or labeler from distributing additional patient-labeling pieces to the dispenser.

(3) In the case of progestational drug products for injection, each package shall include a sufficient number of patient-labeling pieces for the volume of the vial, and instructions to the practitioner administering the drug to give one patient-labeling piece to each premenopausal woman, except those in

whom childbearing is impossible, receiving the drug.

(4) This section does not apply to oral dosage forms labeled solely for the treatment of advanced cancer.

(5) Any progestational drug product, except as noted in paragraphs (d) and (e)(4) of this section, that is not labeled as required by this section and is either introduced or delivered for introduction into interstate commerce, or held for sale after shipment in interstate commerce, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act. However, a progestational drug product in the possession of a wholesaler or retailer before December 12, 1978, is not misbranded if adequate numbers of copies of the patient labeling are furnished to the wholesaler or retailer to permit any retail purchaser after that date to obtain such labeling with the product. The requirement that any progestational drug product be dispensed with patient labeling, as applied to physicians who dispense or administer the drug, will not be effective for supplies in their possession on the effective date, but will apply only to supplies received thereafter.

(f) The Food and Drug Administration has available guideline patient labeling for progestational drug products that includes information responsive to all items specified in paragraph (b) of this section. This labeling was published in a separate notice appearing in the FEDERAL REGISTER of January 12, 1989. Any person may rely on this labeling as complying with paragraph (b) of this section.

(g) Holders of approved new drug applications for progestational drug products that are subject to the requirements of this section shall submit supplements under §314.70(c) of this chapter to provide for the labeling required by paragraph (a) of this section.

[43 FR 47181, Oct. 13, 1978, as amended at 46 FR 53657, Oct. 30, 1981; 54 FR 1163, Jan. 12, 1989]

§ 310.517 Labeling for oral hypoglycemic drugs of the sulfonylurea class.

(a) The University Group Diabetes Program clinical trial has reported an association between the administration of tolbutamide and increased cardiovascular mortality. The Food and Drug Administration has concluded that this reported association provides adequate basis for a warning in the labeling. In view of the similarities in chemical structure and mode of action, the Food and Drug Administration also believes it is prudent from a safety standpoint to consider that the possible increased risk of cardiovascular mortality from tolbutamide applies to all other sulfonylurea drugs as well. Therefore, the labeling for oral hypoglycemic drugs of the sulfonylurea class shall include a warning concerning the possible increased risk of cardiovascular mortality associated with such use, as set forth in paragraph (b) of this section.

(b) Labeling for oral hypoglycemic drugs of the sulfonylurea class shall include in boldface type at the beginning of the ''Warnings'' section of the labeling the following statement:

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes,* 19 (supp. 2): 747–830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of (name of drug) and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply